

**Table S2** Input parameters used in the development of 4-ene-VPA PBPK model

Parameter	Input value	Reference/comment
Physicochemical and blood binding		
Molecular Weight (g/mol)	142.2	PubChem
LogP <sub>o:w</sub>	2.21	ALOGPS
pK <sub>a</sub>	5.06	ChemAxon
B:P	0.55	(no measured data; assumed to be the same as VPA)
f <sub>u</sub>	0.056704	Simcyp predicted
Plasma binding protein	HSA	
Distribution		
Distribution model	Minimal PBPK	
V <sub>ss</sub> (L/kg)	0.209	Simcyp optimized based on Singh <i>et al.</i> , 1988 <sup>[24]</sup>
Elimination		
Elimination model	<i>In vivo</i> clearance	
Cl <sub>iv,4-ene-VPA</sub> (L/h)	2.601	Simcyp optimized based on Singh <i>et al.</i> , 1988 <sup>[24]</sup>
Cl <sub>add</sub> (L/h)	0.3414	Simcyp optimized based on Singh <i>et al.</i> , 1988 <sup>[24]</sup>
Cl <sub>R</sub> (L/h)	2.2596	Simcyp optimized based on Singh <i>et al.</i> , 1988 <sup>[24]</sup>

B:P, blood-to-plasma ratio; Cl<sub>add</sub>, additional systemic clearance; Cl<sub>iv</sub>, intravenous clearance; Cl<sub>R</sub>, renal clearance; f<sub>u</sub>, fraction absorbed; HSA, human serum albumin; k<sub>a</sub>, absorption rate constant; LogP<sub>o:w</sub>, octanol-water partition coefficient; pK<sub>a</sub>, negative log of the acid dissociation constant; V<sub>ss</sub>, volume of distribution at steady state.